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The role of codeine phosphate premedication in fibre-optic bronchoscopy under in sufficient local anaesthesia and midazolam sedation

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Midazolam is widely used as a sedative agent to produce amnesia in patients undergoing fibre-optic bronchoscopy. However, if a patient does not receive sufficient local anaesthesia, continuous severe cough and physical movement may interrupt the procedure and reduce its safety. We therefore examined whether codeine phosphate is a useful premedication for bronchoscopy. The study design was a randomized comparison between codeine phosphate and a placebo in patients undergoing light local anaesthesia and midazolam sedation. We used low dose local anaesthesia (5 ml of nebulized 2% xylocaine) on the assumption of insufficient local anaesthesia. Patients were allocated to receive codeine phosphate 0·4 mg kg^{-1} or a saline placebo 60 min before they were sedated with i.v. midazolam. If the patients exhibited severe cough during bronchoscopy, intrabronchial supplemental local anaesthesia (2% xylocaine solution in 1 ml increments) was instilled via a bronchoscope to the trachea and segmental bronchi to suppress the cough. The dose of supplemental xylocaine was assessed and the requirements were significantly lower in the codeine group compared to the placebo group: 36·4 ± 10·2 mg *vs.* 95·1 ± 24·6 mg, respectively. After bronchoscopy, patients were interviewed by a doctor to assess their willingness to undergo a repeat procedure if one was clinically indicated, but no significant difference was observed between the two groups. If local anaesthesia is insufficient, midazolam together with codeine phosphate premedication is useful for both the patient and the bronchoscopist.

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Introduction

Midazolam is widely used as a sedative agent in patients undergoing fibre-optic bronchoscopy (1). However, the effect of midazolam as an anti-tussive agent is limited. Severe cough and body movements occur during bronchoscopy, especially in patients that cannot inspire enough and reject the inspiration of xylocaine spray as a localized anaesthetic. Codeine phosphate is frequently used as an anti-tussive agent, and we examined the usefulness of this drug as a premedication for bronchoscopy. The aim of this study was to assess the anti-tussive effect of codeine phosphate under midazolam sedation during bronchoscopy.

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Patients and Methods

Of 165 patients undergoing routine diagnostic fibre-optic bronchoscopy without transbronchial biopsy and brushing, 89 consented to enter a consecutive double-blind study to compare codeine phosphate premedication with a saline placebo. Indications of bronchoscopy included productive cough, haemoptysis or bronchogenic neoplasm. Bronchoscopy was performed in Ishikawa Prefectural Central Hospital and Nakamura Hospital. A flexible fibre-optic bronchoscope (Olympus BF-1T30, 1T200; OD, 6 mm) was introduced orally using a mouthpiece. All patients received 0·5 mg of i.v. atropine 30 min before bronchoscopy. The patients in the codeine group received codeine phosphate, 0·4 mg kg^{-1} 60 min before bronchoscopy, while the patients in the placebo group received a saline solution. After 5 ml of nebulized 2% xylocaine as a light local anaesthetic had been administered to the oropharynx, all patients received midazolam, 0·15 mg kg^{-1} i.v. over 30 s. Arterial blood gas analysis was performed in all patients before bronchoscopy. Patients with PaO_2 <70 Torr, $PaCO_2$ >60 or SaO_2 <85% in room air (FIO_2=21%) were excluded as midazolam sedation was not indicated.

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TABLE 1. Patient characteristics. Sex, age, body weight and blood gas analysis of patients in a placebo-controlled comparison of codeine phosphate premedication during fibre-optic bronchoscopy

	Codeine (n=44)	Placebo (n=45)	P-value
Men/women	23/21	20/25	
Mean age (years)	64·3 ± 11·6	66·7 ± 9·7	n.s.*
Mean weight (kg)	48·5 ± 17·6	50·8 ± 17·9	n.s.
$PaCO_2$ (Torr)	42·3 ± 4·6	42·9 ± 3·8	n.s.
PaO_2 (Torr)	81·3 ± 10·3	82·8 ± 8·7	n.s.
O_2 sat (%)	94·9 ± 2·1	95·58 ± 1·2	n.s.

Statistical analysis was carried out using the Mann–Whitney U-test. (Mean values ± SD).
*n.s., not significant.

TABLE 2. Oxygen saturation profile, supplemental local anaesthesia and the number of patients willing to undergo repeat examinations

	Codeine (n=45)	Placebo (n=44)	P-value
SaO_2 <90% (n)	4/45	14/44	<0·05
SaO_2 <85% (n)	0/45	1/44	n.s.*
Mean lowest oxygen	93·8 ± 4·8	91·5 ± 2·4	<0·05
Xylocaine additional (mg)	36·4 ± 10·2	95·1 ± 24·6	<0·01
Willingness to repeat (n/total)	32/45	28/44	n.s.

Statistical analysis was carried out using the Mann–Whitney U-test and chi-squared test.
*n.s., not significant.

Monitoring during bronchoscopy included continuous electrocardiographical (ECG) recording, pulse oximetry and automatic blood pressure recording. At midazolam administration, if patients exhibited an oxygen saturation of <92%, 0·4 mg i.v. fulmazenil was immediately administered. Supplemental oxygen (2 l min^{-1}) was routinely given via a nasal cannula to all patients. If patients exhibited severe cough, intrabronchial supplemental local anaesthesia (2% xylocaine solution in 1 ml increments) was instilled via the bronchoscope to the trachea and segmental bronchi to suppress the cough. The dose of supplemental local anaesthesia required was noted for each patient. After bronchoscopy, patients were administered i.v. fulmazenil, 0.4 mg and assessed by a doctor regarding how comfortable they had been during bronchoscopy and their willingness to undergo a repeat procedure if one was clinically indicated.

Statistical analysis was performed using the Mann–Whitney U-test and chi-squared test.

Results

A total of 89 patients were studied, 45 of whom received codeine phosphate and 44 of whom received a saline solution as a placebo. There were no significant differences between the codeine group and the placebo group in terms of age, PaO_2, $PaCO_2$ or oxygen saturation in room air (Table 1). Bronchoscopic procedures were performed to observe the respiratory tract in most patients, but bronchoalveolar lavage was performed in nine patients in both groups. The mean injection dose of midazolam was 5·0 ± 2·5 M and the induction time was 90–160 s. Three patients showed verbomania and one patient hiccups. Blood pressure and heart rate remained stable. Oxygen desaturation was noted in both groups. There was a significant difference in the number of patients whose oxygen saturation was <90% on at least one occasion during the procedure, but only one patient showed saturation <85%. Concerning the mean lowest oxygen, the codeine group showed a significantly higher value. All patients were amnesiac regarding the procedure. The hiccups disappeared during the procedure. The dose of supplemental local anaesthetic requirements was significantly lower in the codeine group compared to the placebo group, 36·4 ± 10·2 mg *vs.* 95·1 ± 24·6 mg, respectively. However, there was no significant difference in the number of patients willing to repeat the procedure between the two groups (Table 2).

Discussion

We consider that the most important factor for safe bronchoscopic examination is complete local anaesthesia of the airway. Hatton *et al.* (2) suggested that sedation was not significantly more effective than a placebo regarding patient comfort or their willingness to undergo a repeat procedure. They concluded that routine sedation is of little use for patients undergoing single diagnostic fibre-optic bronchoscopy. However, our results showed that sedation is essential even in single diagnostic procedures. In particular, patients who demonstrate a strong pharyngoreflex, nervousness (including children), or a past history of painful bronchoscopy are considered to require sedation. Some of our patients with strong pharyngoreflexes could not continuously inhale local anaesthetic drugs such as xylocaine spray due to severe cough. These patients noted pain during the procedure because the local anaesthesia was incomplete. Therefore, we consider sedation to be important.

Midazolam is well established and widely used as a sedative agent in patients undergoing fibre-optic examination. Midazolam produces amnesia and anxiolytic effects, so patients undergoing bronchoscopy do not feel pain during the procedure. Doses of i.v. midazolam ($0{\cdot}07\ mg\ kg^{-1}$) suggested for sedation may not produce complete amnesia as reported, as mentioned above (2). William *et al.* (3) suggested that higher doses, mean $0{\cdot}24\ mg\ kg^{-1}$, of midazolam produce complete amnesia without serious problems. In this study, we used $0{\cdot}15\ mg\ kg^{-1}$. This dose produced sufficient amnesia, as no patient remembered any situation during bronchoscopy. Based on our experience, incomplete local anaesthesia induces severe cough and physical movement during bronchoscopy even under midazolam sedation. Therefore, bronchoscopy is difficult unless supplemental local anaesthesia is employed. Midazolam is a useful sedative agent but does not exhibit anti-tussive effects (4). Therefore, we used codeine phosphate as a premedication to repress induced cough and physical movement.

In our study, the dose of supplemental local anaesthesia required was significantly lower in the codeine group than in the placebo group. Codeine phosphate was effective to repress induced cough during the procedure. The functional expression time of this drug is 30 min after oral medication, and the drug is effective for more than 90 min. Therefore, the patients received codeine phosphate 60 min prior to bronchoscopy.

Oxygen desaturation was noted when the patients exhibited productive coughing. The number of patients whose lowest saturation was under 90% was significantly higher in the placebo group compared to the codeine group. The codeine group showed a significantly higher value of the mean lowest oxygen. This result indicates that the antitussive effect of codeine phosphate was effective during bronchoscopy. However, there was no significant difference in the number of patients willing to undergo the same examination if necessary. No patient remembered coughing during bronchoscopy because midazolam causes amnesia. The findings showed that bronchoscopy can be performed more easily and safely using codeine phosphate.

It has been reported that sedation for bronchoscopy is associated with major complications (5,6). Severe side-effects of midazolam include depression of the root of the tongue, apnoeic pause, hypopnoea and anaphylactic shock. Only one case exhibited apnoeic pause and the patient was not hypoxycemic or hypercapnic. However, tracheal auscultatory sound was suspected to be stenotic due to tracheal invasiveness of thyroid cancer recurrence. Sedation is contraindicated for patients with forced respiration due to central airway obstruction despite good results of arterial blood gas analysis. Monitoring the ECG, pulse oximetry and blood pressure during bronchoscopy are essential, and we strongly recommend breathing bag or tracheal intubation preparation for unexpected respiratory pause. Moreover, we prepare fluamzenil in a syringe for urgent reversal of sedation before administering midazolam.

We conclude that codeine phosphate is effective in repressing induced coughing during bronchoscopy. Midazolam is a useful sedative agent to produce amnesia in patients who exhibit incomplete local anaesthesia. Premedication codeine phosphate is beneficial for both the patient and bronchoscopist.

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